REMARKS/ARGUMENTS

Applicants' representatives, Darryl Webster, Heather Ettinger, and the undersigned, thank Examiners Reynolds, Achutamurthy, and Pak for the courtesies extended during the telephonic interview on September 30, 2005. During that interview, the rejections under the written description and enablement requirements were discussed. Proposed claim amendments, which are set forth in the instant Amendment and Response, were discussed with the Examiner. Specific issues addressed during the interview are pointed out where appropriate in the arguments.

Claims 8-15, 17-29, 37-41, and 45-68 are pending in the application. In the Office Action mailed June 7, 2005, the Examiner withdrew claims 21-29, 37-41, 45, and 46 from consideration. Claims 8-10, 13-15, 17-20, 47-57, and 62-68 stand rejected and claims 11, 12, and 58-61 stand objected to.

By this Amendment and Response, claims 8-15, 17-29, 37-41, and 45-68 are cancelled without prejudice or disclaimer and new claims 69-95 are added. The new claims correspond to the claims as filed or as previously pending and, where amended, are supported by the specification, per the following table.

New Claim	Prior Claim	Support in the Specification
69	8	Support for "95% sequence similarity" may be found, for example, at p. 8, line 22.
70	8	
71	50	
72	9	

73	11	
74	58	
75	12	
76	60	
77	13, 8	Support for "95% sequence similarity" may be found, for example, at p. 8, line 22.
78	13, 8	
79	13, 11	
80	13, 12	
81	67	
82-85	15	
86-89	17	
90	18	Support for "highly stringent conditions of 0.2x SSC at 68°C; 50% formamide, 4xSSC at 42°C; or under conditions that afford levels of hybridization equivalent to those observed under either of these two conditions" may be found, for example, at p. 20, lines 2-4.
91	19	
92	56	
93	57	
94	20	
95	65	Support for "highly stringent conditions of 0.2x SSC at 68°C; 50% formamide, 4xSSC at 42°C; or under conditions that afford levels of hybridization equivalent to those observed under either of these two conditions" may be found, for example, at p. 20, lines 2-4.

No new matter has been added by way of these claim amendments or new claims.

Rejections under 35 U.S.C. § 102(g)

The Examiner is thanked for notifying Applicants that the previous rejections of claims 8-10, 13-15, 17-20, and 47-55 under 35 U.S.C. § 102(g) are now withdrawn.

Claim Objections

The Examiner has objected to claims 48-50 as being substantial duplicates of claims 47. As these claims have been cancelled, this objection has been deemed moot.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claim 13 and claims 14-15 and 17 depending therefrom under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner contends that the phrase "any combination thereof" in claim 13 is not clear.

By the present Amendment and Response, claim 13 has been cancelled, thus rendering this rejection moot. New claims 77-80, which are directed to the same subject matter as prior claim 13, particularly point out and distinctly claim a vector that encodes a lysyl oxidase. Accordingly, Applicants respectfully submit that this rejection should be withdrawn.

The Examiner has rejected claim 18 and claims 19-20 depending therefrom under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner contends that the phrase "corresponding to" is not clear, arguing that the specification does not describe how one skilled in the art can determine which specific hybridization condition "corresponds to" the condition recited in the claim.

By the present Amendment and Response, claims 18-20 have been cancelled, thus rendering this rejection moot. New claims 90 and 95, and claims 91-94 depending from claim 90, recite "highly stringent conditions of 0.2x SSC at 68°C; 50% formamide, 4xSSC at 42°C; or under conditions that afford levels of hybridization equivalent to those observed under either of these two conditions." Other variations of formamide, SSC, and temperature, or other conditions of salt concentration, chaotropic agent, and temperature could be used to achieve comparable stringency for hybridization, as has been known in the art since at least 1982. (See, for example, Maniatis *et al.*, "Molecular Cloning" (Cold Spring Harbor Laboratories, 1982)). Thus, there is no difference in scope between claims that recite specific hybridization conditions, and claims that recite "corresponding to" such hybridization conditions. However, the claims have been amended as set forth above for grater clarity.

Applicants wish to point out that the claims recite hybridization conditions using "or" as the logical conjunction (*e.g.*, A or B is true if either A is true, B is true, or both are true). It cannot be regarded as an exclusive "or."

Rejections under 35 U.S.C. § 112, first paragraph -- enablement

Claims 8-10, 13-15, 17-20, 47-57, and 62-68 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly non-enabled by the specification.

a. Nucleic acids encoding EER-7 Proteins

With respect to claims 8-10, 13-15, 17, 47-55, 62-64, and 66-68, the Examiner contends that while the specification enables DNA encoding EER-7 of SEQ ID NO: 2, it does not enable "DNA molecules of unlimited structure." In the Office Action, the Examiner argues that claims drawn to nucleotides that encode EER-7 having "75-95% homology to SEQ ID NO: 2 are broader than the scope enabled by the specification." The Examiner states that the "predictability as to the level of conservation between the disclosed sequences and those of other EER-7 is extremely complex" and it would not be routine to screen for polynucleotides with a similar sequence. The Examiner also states "[t]he amino acid sequence determines the structural and functional properties of an enzyme. Knowledge of which sequences can be altered or removed and still result in similar protein activity is well outside the realm of routine experimentation." In the Office Action, the Examiner concludes that it would require undue experimentation to make DNA encoding EER-7 protein different from SEQ ID NO: 2.

Applicants respectfully traverse the stated grounds for rejection and submit that the entire scope of the claims is fully supported by an enabling disclosure. For example, the specification describes EER-7, a novel lysyl oxidase (LO) protein. The specification also fully describes the family of related proteins to which EER-7 belongs, along with their shared function and sequence similarities. The specification contains a full working example of the identification of EER-7 (Example 1, specification, page 44, line 26 to page 47, line 24) as well as the expression of EER-7 and its sequence analysis (Example 2, page 47, line 25 to page 48, line 29). The

sequence analysis of the EER-7 protein establishes its structural similarity with other members of the LO and LOL family, which includes a shared, characteristic catalytic domain associated with LO and LOL proteins, as well as a shared sequence similarity with EER-7 from other species. *See* specification, page 47, lines 21-23; page 48, lines 15-20; Figures 1 and 2. The structural and functional characteristics of the EER-7 protein also distinguish it from the related LOs and LOLs, *e.g.,* the existence of four SRCR domains and the regulation of EER-7 by estrogen. *See* specification, page 4, lines 9-11 and 17-19. Thus, the specification contains working examples that support the making and using of the claimed invention.

The specification contains additional guidance beyond that found in the examples, although well within the skill in the art, including more data on the sequence similarity of the members of the protein family (specification, page 4, lines 13-26; page 8, line 27 - page 9, line 8-10), the function of the members of the family (specification, page 9, line 9-10), and methods to obtain and use the nucleic acids of the invention (specification, page 21-29).

Nonetheless, Applicants note that, by the present Amendment and Response, each of claims 8-10, 13-15, 17, 47-55, 62-64, and 66-68 has been cancelled and replaced, as indicated in the table above, by corresponding claims 69-72 and 77-89. Each of claims 70-72 and 77-89 recite the limitations of claim 69. By the present Amendment and Response, new claim 69 provides an isolated nucleic acid encoding an endothelial estrogen regulated gene-7 protein that has "(i) an amino acid sequence which has at least about 95% sequence similarity with SEQ ID

NO: 2...." [Underscore added]. The Examiner reviewed this claim language prior to the interview and indicated that the specification enables this claim language.

Applicants respectfully submit that the language introduced into the newly presented claims is fully supported by the specification as filed and the full scope of these claims may be achieved by a person of skill in the art with no more than routine experimentation. Applicants believe that the newly amended claims obviate the Examiner's present bases for rejection under 35 U.S.C. § 112, first paragraph and that the claims, as newly presented, are in condition for allowance. Applicants, therefore, request that the Examiner issue a Notice to that effect.

b. Oligonucleotides

With respect to claims 18-20, 56-57, and 65, the Examiner contends that an oligonucleotide of 20 base pairs will hybridize to a wide range of polynucleotides and that the specification does not teach how to use these varying oligonucleotides.

Applicants note that, by the present Amendment and Response, each of claims 18-20, 56-57, and 65 has been cancelled and replaced, as indicated in the table above, by corresponding claims 90-95. Each of claims 91-94 recite the limitations of claim 90. By the present Amendment and Response, new claims 90 and 95 provide isolated oligonucleotides containing "a sequence of at least 20 consecutive nucleotides of SEC ID NO: 1 that hybridizes under highly stringent conditions of 0.2x SSC at 68°C; 50% formamide, 4xSSC at 42°C; or under conditions that afford levels of hybridization equivalent to those observed under either of these two

conditions." [Underscore added]. The amendment has been made, pursuant to Examiner Reynolds' suggestion during the interview, to recite that the 20 consecutive nucleotides from SEC ID NO: 1 mediate hybridization to the target (SEQ ID NO: 1). An oligonucleotide that does not hybridize is not within the scope of this claim, and therefore enablement of such an oligonucleotide is not at issue.[1] If the oligonucleotide is larger than 20 nucleotides, the additional sequence may be fully or partially complementary to SEQ ID NO: 1, so as to contribute to hybridization, or it may provide some other functionality, such as a ribosome (*see, e.g.,* the Specification at page 20, line 18).

The claims, as now presented, are directed to oligonucleotides of no more than 100 nucleotides, with at least 20-30 consecutive nucleotides of SEQ ID NO: 1 that hybridize under highly stringent conditions to a nucleic acid with the sequence of SEQ ID NO: 1. Highly stringent conditions are recited as corresponding to "0.2x SSC at 68°C; 50% formamide, 4xSSC at 42°C; or under conditions that afford levels of hybridization equivalent to those observed under either of these two conditions." Applicants submit that, under highly stringent conditions, oligonucleotides of 20 base pairs will hybridize with a high degree of specificity and,

[1] During the interview, the Examiners suggested that the oligonucleotide could conceivably hybridize to another nucleic acid, but could not explain why that would matter if the oligonucleotide also hybridized to a nucleic acid of SEQ ID NO:1. Applicants are still uncertain what difference this makes. The Examiners offered the explanation that it would be uncertain whether such a hypothetical oligonucleotide were binding to a nucleic acid of SEQ ID NO:1 or to another nucleic acid in, for example, an *in situ* assay. This hypothetical presupposes that a person of unusually low or no skill in the art was conducting the hybridization assay. A person of ordinary skill in the art, who would know the sequence of the oligonucleotide with dual functionality for hybridizing to SEQ ID NO:1 and some other activity, would control for that other activity, *e.g.*, labeling or association with an immobilized sequence. There is no doubt that a person of ordinary skill in the art could introduce other functionality into an oligonucleotide that hybridizes to SEQ ID NO:1.

consequently, that these claims do not contemplate such a wide range of polynucleotides as the Examiner contends.

The specification sets forth how oligonucleotides, according to the scope of the instant claims, can be made (page 20, lines 5-17; page 20, line 28 to page 21, line 22) and describes specific examples of "highly stringent" conditions (specification, page 20, lines 2-4). The claims themselves provide guidance to a skilled artisan as to how to make and use the oligonucleotides of the invention. The claims recite the length of consecutive base pairs and the sequence to which claimed oligonucleotides bind under highly stringent hybridization conditions.

Applicants further point out that oligonucleotide hybridization is a well-established phenomenon that is routinely used in the field of molecular biology. In fact, the use of oligonucleotides to bind and screen for nucleic acids has been known in the art for over 20 years. *See* specification, page 12, line 2.

The amount of experimentation necessary to make and use the claimed oligonucleotides is routine, given the guidance in the specification and claims, the state of the art, and the high level of skill in the art. It is routine to synthesize oligonucleotides of up to 100 nucleotides that have at least 20-30 consecutive base pairs of a disclosed sequence and then screen the oligonucleotides to see if they hybridize under the highly stringent conditions as set forth in the claims.

Applicants respectfully submit that the newly presented claims obviate the Examiner's present bases for rejection under 35 U.S.C. § 112, first paragraph, that each of the newly

presented claims is fully enabled by the specification, and that each of claims 90-95 is in condition for allowance. Applicants, therefore, respectfully request that the Examiner issue a Notice to that effect.

Rejections under 35 U.S.C. § 112, first paragraph -- written description

a. Oligonucleotides

Claims 13, 18-20, 56-57, and 65 stand rejected under 35 U.S.C. § 112, first paragraph. The Examiner alleges that these claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the present application was filed.

As indicated above, with the present Amendment and Response, each of claims 13, 18-20, 56-57, and 65 has been cancelled and the subject matter of those claims presented, in amended form, with newly presented claims 77-80 and 90-95. Of those claims, claims 90-95 are directed to oligonucleotides; claims 77-80 are directed to vectors comprising isolated nucleic acids encoding endothelial estrogen regulated gene-7 proteins. Thus, Applicants believe that the present bases for rejection are properly directed exclusively to claims 90-95, not to claims 77-80.

Applicants respectfully submit that each of these newly presented claims 90-95, which recite that hybridization is mediated by the at least 20 (or 30) consecutive nucleotides from SEQ ID NO:1 in accordance with Examiner Reynolds' suggestion, is fully supported by the specification so as to convey to one skilled in the art that Applicants were, in fact, in possession of the claimed invention at the time the application was filed.

The Examiner alleges that the specification does not contain any disclosure of the function of all the oligonucleotides that consist of any 20-30 nucleotides of SEQ ID NO: 1 and that the genus of these polynucleotides that comprise these oligonucleotides is large and variable. As a consequence, the Examiner believes that many functionally unrelated oligonucleotides are encompassed within the scope of these claims.

As noted above, Applicants point out that claims 90-95 are not directed to all oligonucleotides that comprise (claims 90-94) or consist essentially of (claim 95) a sequence of at least 20 consecutive nucleotides of SEQ ID NO: 1. Each of these claims further recite that the claimed oligonucleotide hybridizes to SEQ ID NO: 1 under highly stringent conditions. Thus, Applicants respectfully disagree with the Examiner's assertion that "the genus of these polynucleotides that comprise these oligonucleotides is large and variable." On the contrary, as will be appreciated by the skilled artisan, the genus of oligonucleotides that fall within the scope of these claims is restricted to that subset of oligonucleotides that possess the claimed structure and function -- that is, that comprise or consist essentially of at least 20 consecutive nucleotides of SEQ ID NO: 1 and that are capable of hybridizing under highly stringent conditions.

It is well known in the art and is set forth in the specification that hybridization of nucleic acids under highly stringent conditions requires a substantial degree of sequence identity and precludes nucleic acids that are structurally and, consequently, "functionally unrelated." *See* specification, page 19, lines 16-18. A person of skill in the art would, therefore, recognize that Applicant was, in fact, in possession of the full range of oligonucleotides either comprising or

consisting essentially of at least 20 consecutive nucleotides of SEQ ID NO: 1 that hybridize under highly stringent conditions to SEQ ID NO: 1. Thus, the Examiner's assertion that many functionally unrelated oligonucleotides are encompassed within the scope of these claims is simply not consistent with the express language of the claims and the understanding of those skilled in the art.[2]

It is well settled by The Court of Appeals for the Federal Circuit and embraced by the USPTO in its Written Description Guidelines that genus claims to nucleic acids based on their hybridization properties are adequately described if they hybridize under highly stringent conditions to known sequences because "such conditions dictate that all species within a genus will be structurally similar." *Enzo Biochem.*, 296 F.3d at 1327 quoting *Guidelines,* Example 9, at 35-37. These hybridization conditions establish the structural similarity between the claimed genus of oligonucleotides comprising or consisting essentially of at least 20 consecutive nucleotides of SEQ ID NO: 1. Because the presently claimed oligonucleotides hybridize to SEQ ID NO: 1 under "highly stringent" conditions as defined in the specification and accepted in the art (*See* specification page 20, lines 1-2), Applicants' claims 90-95 fully comply with the Patent Office Guidelines and Federal Circuit case law.

During the interview, the Examiners explained that in their view, the specification allegedly did not provide a written description with respect to the up to 80 nucleotides potentially

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[2] The Examiner's attention is directed to the issues discussed in footnote 1, *supra*, which relate to written description as well as enablement. Thus, the applicant need only describe what is claimed; one of skill in the art knows, in light of that description, how to employ the claimed subject matter to his or her own ends.

present on an oligonucleotide having the recited sequence of 20 (or 30) nucleotides of SEQ ID NO: 1.[3] The Examiners agreed that in an oligonucleotide with a sequence from at least 20 (or 30) nucleotides of SEQ ID NO: 1 (and thus complementary to either the (+) or (-) strand of SEQ ID NO: 1), that complementary sequence would mediate hybridization. It is an inherent feature of complementary sequences, and it is fully described.

The term "comprising" means that the claimed subject matter includes, but need not be limited to, the recited subject matter. Considering the limitations of the claims: (i) an oligonucleotide of no more than 100 nucleotide, (ii) containing a sequence of at least 20 consecutive nucleotides of SEQ ID NO:1, (iii) which hybridizes to SEQ ID NO:1, there is no support in either the Office Action, or that arose during the interview, to suggest that any of these limitations are not described. There is no basis in the statute or case law for requiring some function or any function beyond that recited. In particular, speculation about the consequences of other functionality in the unrecited portion of the oligonucleotide has no place in a rejection for lack of written description, because it is not part of the recited invention.[4] One must describe what is claimed. The PTO does not reject nucleic acid vector claims because sequences on the vector constitute "a large variable genus with the potentiality of having any function or no

[3] The Examiners did not consider the more plausible possibility that the sequence of the claimed oligonucleotide would have a sequence that is identical to or substantially identical to a corresponding portion of SEQ ID NO:1. Such oligonucleotides have well-known uses, such as for hybridization, PCR priming, regulating expression (e.g., antisense oligonucleotides), detecting polymorphisms, introducing site-directed mutations, and other uses that are so well-established in the art they require no elaboration here. Notwithstanding the well-known, established uses in the art for oligonucleotides, and thus the intrinsic structural features of such oligonucleotides, the Specification elaborates on this issue in detail. *See* page 20, line 5 to page 21, line 22.

[4] Nevertheless, the Specification provides a description of oligonucleotides capable of hybridizing to a nucleic acid of SEQ ID NO:1 that have additional functionality, such as ribozymes. Specification, page 20, line 18.

function." Similarly, one may claim a host cell comprising this vector, much of which is nucleic acid sequence *terra incognita*, despite the fact that the host cell contains functionally unrelated nucleic acids (e.g., the host cell genome), not to mention an abundance of structurally unrelated proteins, lipids, carbohydrates, RNA, and organic and inorganic molecules.

Thus, this rejection represents an inexplicable and legally erroneous departure from established law as it relates to claiming inventions, particularly bearing in mind that the oligonucleotide must hybridize to SEQ ID NO: 1. The Examiner seemed to have "read in" limitations to the oligonucleotide that are not recited in order to then assert that the specification does not provide a written description of those limitations. The claims as amended address this concern by explicitly tying the structure (a sequence of at least 20 (or 30) consecutive nucleotides of SEQ ID NO:1) with the function inherent to that structure (hybridization under highly stringent conditions). If, in view of the present amendment, the Examiner continues to allege that this is a proper basis for rejecting the claim, the Examiner must provide the legal reasoning in support of the rejection.

Applicants respectfully submit that instant claims 90-95 are supported by a specification that reasonably conveys to the skilled artisan that Applicants were in possession of the claimed invention at the time the present application was filed and that the present bases for rejection may properly be withdrawn and claims 90-95 allowed. Applicants request that the Examiner issue a Notice to that effect.

Allowable Subject Matter

In the Action, the Examiner indicated that claims 11-12 and 58-61 were objected to as being dependent upon a rejected base claim, but that they would be allowable if rewritten in independent form. Applicants respectfully point out that although claims 11-12 and 58-61 have been cancelled, new claims 73, 75, 74, and 76 correspond to claims 11-12, 58, and 60, respectively. Accordingly, it is respectfully requested that these claims be deemed allowable.

Conclusion

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue. If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Dated: December 6, 2005

Respectfully submitted,

By _____ Reg. No. 51,058
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